Title: The Neurophysiology of Paediatric Movement Disorders

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Abstract

Purpose of review

To demonstrate how neurophysiological tools have advanced our understanding of the pathophysiology of paediatric movement disorders, and of neuroplasticity in the developing brain.

Recent findings

Delineation of corticospinal tract connectivity using Transcranial Magnetic Stimulation (TMS) is being investigated as a potential biomarker for response to therapy. TMS measures of cortical excitability and neuroplasticity are also being used to investigate the effects of therapy, demonstrating neuroplastic changes that relate to functional improvements. Analysis of evoked potentials and event-related changes in the EEG spectral activity provide growing evidence for the important role of aberrant sensory processing in the pathophysiology of many different movement disorders. Neurophysiological findings demonstrate that children with clinically similar phenotypes may have differing underlying pathophysiology, which in turn may explain differential response to therapy. Neurophysiological parameters can act as biomarkers, providing a means to stratify individuals, and are well suited to provide biofeedback. They therefore have enormous potential to facilitate improvements to therapy.

Summary

Although currently a small field, the role of neurophysiology in paediatric movement disorders is poised to expand, both fuelled by and contributing to the rapidly growing fields of neuro-rehabilitation and neuromodulation and the move towards a more individualized therapeutic approach.

Keywords

Paediatric
Movement disorders
Sensorimotor integration
Transcranial magnetic stimulation
Neuroplasticity

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INTRODUCTION

Movement disorders remain a significant cause of childhood disability, with lifelong implications for the child and society. Understanding the underlying pathophysiology of movement disorders is the key to developing effective therapies and to providing an individualised approach to management.

Significant developments in neurophysiology over the last 20-30 years have advanced scientific knowledge of normal and disordered movement control[1]. However, much of this understanding comes from adult-based studies with far fewer studies in children. Adult findings cannot necessarily be extrapolated to children and dedicated paediatric studies are essential (Table 1).

This review highlights recent neurophysiological research studies in children with movement disorders that have advanced understanding of pathophysiology and neuroplasticity in the developing brain. The term ”movement disorders” can be understood in different ways. This review covers disorders of the central control of movement, including disorders of pyramidal and extra-pyramidal systems, but not disorders of peripheral nerve or muscle. The use of neurophysiological techniques as therapeutic tools (e.g. repetitive Transcranial Magnetic Stimulation or Transcranial Direct Current Stimulation) is beyond the scope of this article but is covered in detail elsewhere[3].

HEMIPLEGIC AND DIPLEGIC CEREBRAL PALSY

Most neurophysiological studies in children to date focus on “spastic” cerebral palsy (CP).

Transcranial Magnetic Stimulation (TMS)

TMS is a non-invasive, painless method of cortical stimulation and has transformed understanding of motor neurophysiology over the past three decades. It is safe and well tolerated in children and has been used to demonstrate maturational changes in corticospinal tract (CST) function, measures of corticospinal excitability, intra-cortical inhibition and plasticity.

TMS in delineating corticospinal connectivity - a potential biomarker for therapy.

Seminal TMS studies by Eyre[4] and Staudt[5] demonstrated that many children with hemiplegic cerebral palsy (CP) following perinatal brain injury have preserved ipsilateral CST projections from the unaffected hemisphere to the most affected hand, due to activity-dependent withdrawal of contralateral projections from the affected hemisphere. Individuals with ipsilateral or a mixed/bilateral CST pattern generally have worse hand function than those with preserved contralateral projections[6-8]. Building on this fundamental observation, several groups have sought to determine whether differential responses to therapy in children with hemiplegic CP might reflect their underlying corticospinal connectivity. Some conflicting reports have arisen: Islam et al[9] found children with hemiplegia improved following Constraint Induced Movement Therapy (CIMT) regardless of their underlying CST connectivity. This contrasts with a previous study in which individuals with ipsilateral projections showed less benefit than those with contralateral projections[10]. This discrepancy may reflect differences in patient selection and the outcome measures used. Both studies demonstrate considerable variation in the response between individuals, even within the ipsilateral or contralateral groups.

A more recent study investigated the response to Hand-Arm Bimanual Intensive Training (HABIT) in 33 children with hemiplegic CP[7]. Children with either contralateral or ipsilateral corticospinal connectivity improved to a similar extent with respect to baseline, across four outcome measures. Those with *bilateral* corticospinal projections also improved. The authors concluded that bimanual therapy may therefore be generally applicable to the range of children with hemiplegic CP. Future studies characterising the underlying sensorimotor physiology on an individual basis

may facilitate development of more targeted therapy approaches and maximise the potential functional gains for a given individual. Jaspers et al recently described a framework for a multi-modal delineation of the corticospinal tract, which will facilitate its use as a biomarker for therapy[11]. Exploiting complementary features of imaging and neurophysiology is powerful (Table 2). Incorporating measures of sensory processing, psychological and cognitive factors could strengthen this model further.

TMS and the unlesioned hemisphere in CP

Zewdie et al[8] recently evaluated corticomotor neurophysiology of the contralesional hemisphere in children with unilateral perinatal stroke. One of their most striking observations was the difference in Motor Evoked Potential (MEP) stimulus response curve between groups during conditions of active contraction. Compared with controls, the increase in area under the curve with increasing stimulus intensity during active contraction was significantly smaller in the contralesional side and less affected hand of patients, either with or without ipsilateral projections. The observed alterations in cortical mechanisms involved in activating the less affected hand have important implications for rehabilitation in children with perinatal stroke.

Insights into therapy-driven changes in cortical plasticity

Therapy-induced changes in cortical excitability have been assessed by comparing MEP amplitudes before and after therapy. Juenger et al[12] reported increased motor cortex excitability for those with contralateral but decreased excitability for those with ipsilateral CST projections, following CIMT. In contrast, in a study of changes following HABIT, Bleyenheuft et al[13] found increased motor cortex excitability in two patients, one with contralateral and one with ipsilateral CST connectivity.

More recently, Friel et al[14] used TMS to assess motor cortex excitability and to map the cortical representation of two upper limb muscles before and after bimanual therapy for children with hemiplegic CP, comparing a group who underwent a structured skill training approach, using progressively more difficult tasks, versus an unstructured approach. Whilst both groups showed improvements in bimanual hand

use and dexterity, only the structured skill group showed evidence of significant changes in plasticity. Changes in motor map size correlated with functional improvements, demonstrating the clinical relevance of these cortical changes. Furthermore, plasticity of motor maps was demonstrated regardless of whether they were located in the hemisphere contralateral or ipsilateral to the most affected hand.

Electromyography (EMG) studies have demonstrated plastic changes in the CST following gait training in children with spastic CP. Changes in the strength of tibialis anterior EMG:EMG coherence were positively correlated with improvements in the subjects' ability to lift the toes in the swing phase[15].

Evoked Potentials, Event Related Potentials and Spectral EEG changes – investigating sensory pathways and processing

Neurophysiological studies have also advanced our understanding of the role of sensory abnormalities in the pathophysiology of movement disorders. In a combined neurophysiology and neuroimaging study, Papadelis et al demonstrated altered morphology of somatosensory evoked responses using Magnetoencephalography (MEG) in children with hemiplegic or diplegic CP, along with altered somatotopic organisation of the primary somatosensory cortex (functional MRI findings) and structural deficits in thalamocortical pathways to both pre and post-central gyri (Diffusion Tensor Imaging findings)[16]. Pihko et al also found delayed or altered morphology of somatosensory evoked responses in the lesioned hemisphere of children with hemiplegic CP[17].

Event Related Desynchronisation (ERD) or Synchronisation (ERS) measure non-phase-locked changes in the on-going EEG activity. These reflect a transient decrease or increase, respectively in the on-going rhythmic/oscillatory activity. ERD and ERS are observed in specific frequency bands in response to sensory stimulation or movement and are considered to reflect changes in cortical processing/activation. Several recent studies have identified deviations from these normal patterns in children with cerebral palsy, providing evidence for abnormal cortical processing of sensory information: Kurz[18] used MEG to study cortical activity in response to a tactile stimulus in eight children with spastic CP. Compared with typically

developing children, children with CP had a similar event related increase in alpha-theta frequency activity (4-14Hz), but an *increase* rather than decrease in beta frequency activity (18-34Hz). Similarly, Riquelme[19] showed an *increase* in beta power in response to tactile stimulation in children/young adults with bilateral asymmetrical CP, rather than the typical decrease. Kurz also demonstrated that aberrant alpha range synchronisation in the somatosensory cortices was linked with errors in the performance of an isometric ankle plantar-flexion task in children with diplegic or hemiplegic CP[20], and that the reduced responsiveness of alpha range activity in primary somatosensory cortex was associated with reduced ankle strength, step length and walking speed[21], emphasising the functional relevance of these changes.

Diminished proprioception in children with CP may also impact on motor imagery, as the internal representation of an action. Jongsma et al recently demonstrated impaired motor imagery for the affected hand in children with hemiplegia, with altered Event Related Potentials compared to controls during a Hand Laterality Judgement task[22].

DYSTONIA

Beyond the field of spastic CP, there are far fewer studies in children with other (extrapyramidal*)* movement disorders. The proposed pathophysiological mechanisms of dystonia are based on adult studies. These include evidence of deficient inhibition throughout the nervous system, exaggerated plasticity, disordered sensorimotor integration and pathologically enhanced low frequency oscillatory activity in the basal ganglia-thalamo-cortical network[1,23,24]. However, these studies focus on primary (genetic or idiopathic) dystonia. Individuals with secondary dystonia do not necessarily show the same abnormalities. In particular, adults with hemidystonia secondary to unilateral basal ganglia/thalamic stroke do not show the exaggerated plasticity seen in primary dystonia[25]. Furthermore, the location of basal ganglia lesions appears to influence the changes in corticospinal excitability seen in adults with secondary dystonia[26].

The spectrum of disorders leading to dystonia in childhood is different from that in adulthood, with secondary/acquired dystonia (e.g. dyskinetic CP due to prematurity or

term Hypoxic Ischaemic Encephalopathy) being more common than primary. Disease mechanisms are likely to be different in individuals with an injury/insult to the brain during early development. Accepted models of "normal" sensorimotor control may not be applicable as these networks may be disrupted, re-organised or never fully develop. Lessons learned from hemiplegic CP emphasise this. Significant knowledge gaps in the pathophysiology of childhood dystonia are currently impeding our ability to manage these individuals. A comprehensive, systematic evaluation of neurophysiology in children with dystonia is needed.

TMS to assess CST integrity

McClelland et al[27] previously assessed corticospinal tract integrity in a heterogeneous group of 62 children with dystonia, using TMS to measure Central Motor Conduction Time (CMCT). CMCT was normal in most children studied, including those whose cranial MRI raised suspicion of CST damage. Diffusion Tensor Imaging (DTI) metrics did not correlate with TMS measures of CST integrity[28], emphasizing that neurophysiology and imaging provide different, complementary information (Table 2).

Sensory Evoked Potentials

Our more recent study of a large (>100) cohort of children with dystonia found abnormal Sensory Evoked Potentials (SEPs) were more frequent than CMCT abnormalities, being seen in more than half of those with secondary/acquired dystonia[29]. Importantly, those children with abnormal SEPs or CMCTs who proceeded to Deep Brain Stimulation (DBS) had less benefit than those with normal SEPs or CMCT (McClelland et al unpublished data). However, outcomes still vary widely between individuals, so further predictive markers are needed.

In a recent study of Segawa Disease (autosomal dominant Dopa-responsive Dystonia), which included 2 adolescents, Kimura demonstrated that pre-movement gating of the median nerve SEP was preserved in patients with the predominantly postural dystonia type of Segawa disease (SD-P) but impaired in those with the action dystonia type (SD-A)[30]. Thus even within the same genetic disorder, clinical/phenotypic differences between patients may relate to differences in underlying neurophysiology.

EEG spectral changes

Kukke et al analysed spectral changes in sensorimotor cortex activity during an isometric wrist extension task in individuals with hemidystonia following childhood stroke[31]. They found that typical task-related changes in EEG spectral power were reduced in the ipsilesional hemisphere of patients with dystonia compared with healthy controls. This reduced desynchronisation correlated with reduced force produced by the affected wrist. In addition, coherence between the sensorimotor cortex of the two hemispheres was reduced in the dystonia group compared with controls, and this correlated with poorer function and greater dystonia severity in the affected arm.

EMG studies

A recent study by Lunardini et al recorded joint kinematic and EMG data from upper limb muscles during a simple figure 8 writing task[32]. Children with dystonia (n=7) showed increased EMG activity uncorrelated with the movement task compared with healthy controls, even when the degree of accuracy was similar between groups. If validated in larger studies, this method could potentially provide objective assessment of movement abnormality in childhood dystonia.

Basal Ganglia neuronal activity

McClelland et al[33] report findings from microelectrode recordings of pallidal neurons obtained at the time of DBS surgery in 44 children with dystonia. They show clear differences in pallidal neuronal firing rates and patterns between 14 children with primary dystonia, 22 children with secondary dystonia arising from a static brain lesion and 8 children with neurodegenerative dystonia due to Pantothenate Kinase 2 (PANK2) deficiency. Within the secondary dystonia group, those with perinatal lesions (dystonic cerebral palsy) had the slowest firing rates in the Globus pallidus internus (GPi). The differences in GPi firing patterns correlated with clinical phenotype: those with fixed/static dystonia showed a higher proportion of regularly firing cells while those with phasic/dynamic dystonia showed a higher proportion of irregularly firing cells. Furthermore, GPi cells from the children with PANK2 deficiency showed a predominantly regular firing pattern, in contrast to the other

groups, who showed predominantly irregularly firing cells (Figure 1). Interestingly, mean GPi firing rates correlated with outcome from DBS.

OTHER MOVEMENT DISORDERS

Khedr et al[34] report reduced motor cortex excitability in 16 adolescents and young adults with Sydenham's chorea, using TMS measures. This interesting finding challenges the accepted model that a hyperkinetic disorder will be associated with decreased cortical inhibition/increased excitability. A number of explanations are feasible, including the possibility that compensatory mechanisms are at play[35]. On a similar theme, Draper et al[36] demonstrate in ten adolescents with Tourette Syndrome (TS) that changes in motor cortex excitability in advance of movement are not in keeping with those predicted, based on previously proposed models of cortical hyperexcitability and reduced cortical inhibition. Moreover, they find that the rise in MEP amplitude during movement preparation was smallest in those with the greatest clinical severity of tics. They argue that the findings represent the development of compensatory mechanisms to suppress corticospinal excitability, reflecting the observation that most patients with TS are able to gain control over their tics by early adulthood.

Buse et al[37] demonstrate reduced sensorimotor gating in children with TS, using the blink startle reflex in a Pre-pulse Inhibition paradigm (PPI). In healthy controls, the ocular EMG response to a startle stimulus is reduced in those trials where the startle stimulus is preceded by a weaker "prepulse" stimulus, demonstrating pre-pulse inhibition, whereas boys with TS (N=22), showed significantly less pre-pulse inhibition in their ocular EMG response. This observation was paralleled by fMRI changes. The findings provide further evidence that TS is characterised by a heightened sensitivity to external stimuli and impaired ability to suppress a motor response to a sensory stimulus.

CONCLUSION

Neurophysiology in paediatric movement disorders is a neglected field, but significant advances have been made: The contribution of aberrant sensory processing to the underlying pathophysiology of disorders previously regarded as having "pure motor" phenomena is much greater than previously appreciated, with evidence for abnormal sensorimotor integration across a range of movement disorders. This has important implications for therapy. Studies in hemiplegia demonstrate that perinatal brain lesions can lead to activity-dependent reorganisation of sensorimotor pathways, clear justification that we cannot assume previously accepted models of normal sensorimotor networks, based on adult studies, to apply in paediatric movement disorders. More work in this area is therefore urgently needed. Although children with movement disorders can be difficult to study, neurophysiological recordings are non-invasive, well-tolerated and can be suitable for biofeedback (Table 2) so the field is poised for expansion. Many factors point towards early intervention as a means to maximize benefit following perinatal brain injury, particularly in the growing field of neuromodulation. A thorough, systematic evaluation of sensorimotor neurophysiology during normal development and following early brain injury will be both a prerequisite to, and an integral part of, the implementation of such programmes.

Key Points

The neurophysiology of paediatric movement disorders is an under-researched area, with most studies focusing on hemiplegic CP and few on other conditions.

Neurophysiological studies have provided significant insights into the pathophysiology of movement disorders.

TMS has been used to demonstrate changes in corticospinal connectivity and excitability in movement disorders and evidence of neuroplasticity in the developing or injured brain.

Evoked potentials and Event Related changes in spectral EEG activity have provided evidence of abnormal sensory processing/sensorimotor integration in a range of paediatric movement disorders

Neurophysiological tools provide objective evidence of nervous system function and have great potential for use as biomarkers and/or for biofeedback as technologies develop.

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Conflicts of Interest

None

References

1. Hallett M, Rothwell J. Milestones in clinical neurophysiology. Mov Disord. 2011;26(6):958-67.

* 2. Millar LJ, Shi L, Hoerder-Suabedissen A, et al. Neonatal Hypoxia Ischaemia: Mechanisms, Models, and Therapeutic Challenges. Front Cell Neurosci. 2017;11:78.
Detailed review of mechanisms of neonatal hypoxic ischaemic injury, a significant cause of movement disorders in children. Explains the importance of the sub-plate in thalamocortical development.

* 3. Kirton A. Advancing non-invasive neuromodulation clinical trials in children: Lessons from perinatal stroke. Eur J Paediatr Neurol. 2017;21(1):75-103.
This is a comprehensive review of therapeutic neuromodulation in children and emphasises the rigor in experimental design, patient selection and methodology that is needed in exectuing succesful and meaningful clinical trials in this field.

4. Eyre JA, Taylor JP, Villagra F, et al. Evidence of activity-dependent withdrawal of corticospinal projections during human development. Neurology. 2001;57(9):1543-54.

5. Staudt M, Grodd W, Gerloff C, et al. Two types of ipsilateral reorganization in congenital hemiparesis: a TMS and fMRI study. Brain. 2002;125(Pt 10):2222-37.

6. Baranello G, Rossi Sebastiano D, Pagliano E, et al. Hand function assessment in the first years of life in unilateral cerebral palsy: Correlation with neuroimaging and cortico-spinal reorganization. Eur J Paediatr Neurol. 2016;20(1):114-24.

* 7. Smorenburg AR, Gordon AM, Kuo HC, et al. Does Corticospinal Tract Connectivity Influence the Response to Intensive Bimanual Therapy in Children With Unilateral Cerebral Palsy? Neurorehabil Neural Repair. 2017;31(3):250-60.
This study is the first to investigate the influence of corticospinal connectivity on the response to a bimanual therapy regime in a group of children with hemiplegia and to demonstrate a similar degree of improvement for children with ipsilateral or contralateral projections.

** 8. Zewdie E, Damji O, Ciechanski P, et al. Contralesional Corticomotor Neurophysiology in Hemiparetic Children With Perinatal Stroke. Neurorehabil Neural Repair. 2017;31(3):261-71.
This is the largest study of TMS parameters in children with perinatal stroke and provides a systematic evaluation of motor cortex physiology in the contralesional

hemisphere. The findings demonstrate significant alterations in patterns of activity in the contralesional cortex, with important functional implications for the less affected hand.

9. Islam M, Nordstrand L, Holmstrom L, et al. Is outcome of constraint-induced movement therapy in unilateral cerebral palsy dependent on corticomotor projection pattern and brain lesion characteristics? Dev Med Child Neurol. 2014;56(3):252-8.

10. Kuhnke N, Juenger H, Walther M, et al. Do patients with congenital hemiparesis and ipsilateral corticospinal projections respond differently to constraint-induced movement therapy? Dev Med Child Neurol. 2008;50(12):898-903.

* 11. Jaspers E, Byblow WD, Feys H, et al. The Corticospinal Tract: A Biomarker to Categorize Upper Limb Functional Potential in Unilateral Cerebral Palsy. Front Pediatr. 2015;3:112.

This article provides a detailed review of the impact of early brain injury on the sensorimotor system and proposes a framework for systematic multi-modal evaluation of the corticospinal tract in individual children with unilateral cerebral palsy, to aid stratification for therapy.

12. Juenger H, Kuhnke N, Braun C, et al. Two types of exercise-induced neuroplasticity in congenital hemiparesis: a transcranial magnetic stimulation, functional MRI, and magnetoencephalography study. Dev Med Child Neurol. 2013;55(10):941-51.

* 13. Bleyenheuft Y, Dricot L, Gilis N, et al. Capturing neuroplastic changes after bimanual intensive rehabilitation in children with unilateral spastic cerebral palsy: A combined DTI, TMS and fMRI pilot study. Res Dev Disabil. 2015;43-44:136-49.

This is a detailed case study of two patients, using combined neurophysiological and imaging assessments to provide evidence of neuroplasticity following HABIT in children with CP. Importantly, similar changes were seen in ipsilateral or contralateral CST connectivity.

** 14. Friel KM, Kuo HC, Fuller J, et al. Skilled Bimanual Training Drives Motor Cortex Plasticity in Children With Unilateral Cerebral Palsy. Neurorehabil Neural Repair. 2016;30(9):834-44.

This is the first study to assess the difference in neuroplastic effects induced by structured versus unstructured bimanual therapy. The finding that significant plasticity was observed only with structured skill training has important implications for design of rehabilitation strategies.

15. Willerslev-Olsen M, Petersen TH, Farmer SF, et al. Gait training facilitates central drive to ankle dorsiflexors in children with cerebral palsy. Brain. 2015;138(Pt 3):589-603.
16. Papadelis C, Ahtam B, Nazarova M, et al. Cortical somatosensory reorganization in children with spastic cerebral palsy: a multimodal neuroimaging study. Front Hum Neurosci. 2014;8:725.
17. Pihko E, Nevalainen P, Vaalto S, et al. Reactivity of sensorimotor oscillations is altered in children with hemiplegic cerebral palsy: A magnetoencephalographic study. Hum Brain Mapp. 2014;35(8):4105-17.
* 18. Jongsma ML, Baas CM, Sangen AF, et al. Children with unilateral cerebral palsy show diminished implicit motor imagery with the affected hand. Dev Med Child Neurol. 2016;58(3):277-84.
This is one of few studies to investigate implicit motor imagery using ERP methodology in children and the first to compare the capacity of the affected and less-affected hand in unilateral CP. It highlights the need to remember that children with CP may have an altered internal body schema, which is relevant for rehabilitation strategies.
* 19. Kurz MJ, Becker KM, Heinrichs-Graham E, et al. Children with cerebral palsy have uncharacteristic somatosensory cortical oscillations after stimulation of the hand mechanoreceptors. Neuroscience. 2015;305:67-75.
This is one of few studies to investigate neurophysiological changes in sensory processing in children with CP and raises important questions about the relationship between neural oscillations in different frequency bands.
20. Riquelme I, Padron I, Cifre I, et al. Differences in somatosensory processing due to dominant hemispheric motor impairment in cerebral palsy. BMC neuroscience. 2014;15:10.
21. Kurz MJ, Heinrichs-Graham E, Arpin DJ, et al. Aberrant synchrony in the somatosensory cortices predicts motor performance errors in children with cerebral palsy. J Neurophysiol. 2014;111(3):573-9.
* 22. Kurz MJ, Heinrichs-Graham E, Becker KM, et al. The magnitude of the somatosensory cortical activity is related to the mobility and strength impairments seen in children with cerebral palsy. J Neurophysiol. 2015;113(9):3143-50.

This study shows that abnormalities in sensory processing from lower limb stimulation are associated with reduced ankle strength, step length and walking speed in children with CP, providing evidence for the functional relevance of these changes.
23. Avanzino L, Tinazzi M, Ionta S, et al. Sensory-motor integration in focal dystonia. Neuropsychologia. 2015;79(Pt B):288-300.
24. Neumann WJ, Jha A, Bock A, et al. Cortico-pallidal oscillatory connectivity in patients with dystonia. Brain : a journal of neurology. 2015;138(Pt 7):1894-906.
25. Kojovic M, Parees I, Kassavetis P, et al. Secondary and primary dystonia: pathophysiological differences. Brain. 2013;136(Pt 7):2038-49.
26. Trompetto C, Avanzino L, Marinelli L, et al. Corticospinal excitability in patients with secondary dystonia due to focal lesions of the basal ganglia and thalamus. Clin Neurophysiol. 2012;123(4):808-14.
27. McClelland V, Mills K, Siddiqui A, et al. Central motor conduction studies and diagnostic magnetic resonance imaging in children with severe primary and secondary dystonia. Dev Med Child Neurol. 2011;53(8):757-63.
* 28. Lumsden DE, McClelland V, Ashmore J, et al. Central Motor Conduction Time and Diffusion Tensor Imaging metrics in children with complex motor disorders. Clin Neurophysiol. 2015;126(1):140-6.
This is the only study to compare neurophysiology and imaging assessments of corticospinal tract integrity in children with dystonia.
* 29. McClelland VM, Fialho D, Flexney-Briscoe D, et al. Abnormal Somatosensory Evoked Potentials in Children with dystonia - a potential predictive marker for outcome to Deep Brain Stimulation? Dev Med Child Neurol. 2017;59(Suppl 1):9P.
This is one of few studies reporting neurophysiological findings in children with dystonia and is the first study to demonstrate the potential of SEPs as a predictive marker for outcome from DBS. (Full paper submitted).
* 30. Kimura K, Nagao Y, Hachimori K, et al. Pre-movement gating of somatosensory evoked potentials in Segawa disease. Brain Dev. 2016;38(1):68-75.
This is the first study to compare sensorimotor gating in patients with different forms of autosomal dominant Dopa Responsive Dystonia. It is important because it demonstrates differences in neurophysiological parameters between patients with the same genetic disorder but different clinical phenotypes.

* 31. Kukke SN, de Campos AC, Damiano D, et al. Cortical activation and inter-hemispheric sensorimotor coherence in individuals with arm dystonia due to childhood stroke. Clin Neurophysiol. 2015;126(8):1589-98.
This is one of very few studies investigating the neurophysiology of secondary dystonia and the first to demonstrate abnormalities of task-related spectral EEG changes in this patient population.
* 32. Lunardini F, Maggioni S, Casellato C, et al. Increased task-uncorrelated muscle activity in childhood dystonia. J Neuroeng Rehabil. 2015;12:52.
This study introduces a new method to quantify abnormal muscle activity in children with dystonia.
* 33. McClelland VM, Valentin A, Rey HG, et al. Differences in globus pallidus neuronal firing rates and patterns relate to different disease biology in children with dystonia. J Neurol, Neurosurg, Psychiatry. 2016;87(9):958-67.
This is the only study of pallidal neuronal firing data in children with primary and secondary dystonia. Its important findings include demonstrating clear differences in neuronal firing properties between patients with dystonia of different aetiologies, and that pallidal firing properties relate to both clinical phenotype and to outcome from DBS.
* 34. Khedr EM, Ahmed MA, Ali AM, et al. Changes in motor cortical excitability in patients with Sydenham's chorea. Mov Disord. 2015;30(2):259-62.
This is the first study to demonstrate changes in motor cortical excitability in this patient population and is important because it challenges previously accepted physiological concepts.
35. Hallett M, Obeso J. Where does chorea come from? cortical excitability findings challenge classic pathophysiological concepts. Mov Disord. 2015;30(2):169-70.
* 36. Draper A, Jude L, Jackson GM, et al. Motor excitability during movement preparation in Tourette syndrome. J Neuropsychol. 2015;9(1):33-44.
This study demonstrates reduced corticospinal excitability during movement preparation in adolescents with Tourette Syndrome, the findings correlating with clinical severity. The study highlights that neurophysiological changes may reflect either causative or compensatory mechanisms.

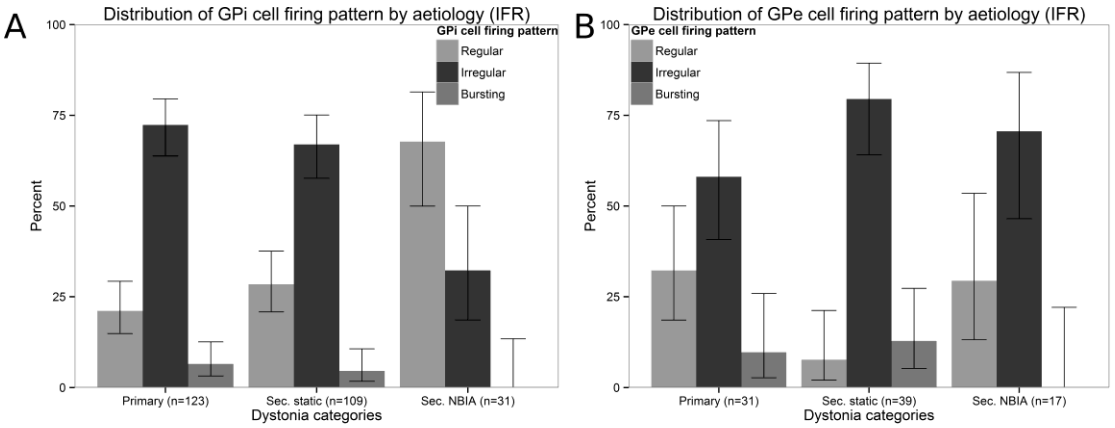
* 37. Buse J, Beste C, Herrmann E, et al. Neural correlates of altered sensorimotor gating in boys with Tourette Syndrome: A combined EMG/fMRI study. World J Biol Psychiatry. 2016;17(3):187-97.
This study provides further evidence that the ability to suppress a motor response to a sensory stimulus is impaired in boys with Tourette Syndrome. The paper highlights the importance of strict sample selection to reduce potential confounding factors.

Table 1

Rationale for dedicated paediatric neurophysiological studies
The sensorimotor system is still developing and maturing through infancy, childhood and adolescence.
Some disorders are encountered solely or more frequently in children than adults.
Accepted models of "normal" sensorimotor control may not be applicable when a brain injury/insult has occurred at an early developmental stage.
The mechanisms underlying a particular disorder may change during the course of development; the presence of transient structures such as the cortical sub-plate[2] imply specific periods of vulnerability to insult.
An insult to the brain in childhood may have different consequences from that in adulthood. e.g. post-stroke dystonia is more common in children than adults.
Some neurophysiological changes observed in adults may represent compensatory changes e.g. as a consequence of prolonged muscle spasms in dystonia.
To understand the effect of critical periods of vulnerability to insult and critical windows of opportunity to early intervention.

Table 2 - Complementarity of imaging and neurophysiology techniques:
Both imaging and neurophysiology techniques have advantages and disadvantages, including those listed here. A multi-modal assessment is therefore ideal.

Neurophysiology **TMS, EEG, MEG, EMG**	**Imaging** **MRI, fMRI, DTI, PET**
Provide information on nervous system function	Provide information on nervous system structure (MRI, DTI) or function (fMRI, PET)
Record brain activity (EEG) or muscle activity (EMG) directly	Assesses function via changes in blood flow (fMRI) or metabolic activity (PET) in relation to brain activity.
No requirement for sedation or general anaesthetic	Sedation or general anaesthetic often needed in children with movement disorders to avoid contamination by movement artefact.
No radioactivity	PET requires injection of radioactive tracer.
Relatively inexpensive	Expensive scanning time
Acquisition time less of a problem	Scan time limited by cost and requirement for sedation
TMS activates predominantly the fastest conducting corticospinal tract fibres	DTI not limited to fastest conducting corticospinal tract fibres
Temporal resolution very good (milliseconds)	Temporal resolution less good (seconds-minutes)
EEG Spatial resolution less good (can be better with MEG)	Spatial resolution very good
Cerebellum and deep structures not easily accessible	Imaging can provide good information about posterior fossa and deep structures
EEG data are recorded in real-time and ambulatory recording is feasible, making neurophysiological signals ideal candidates for biofeedback in closed-loop neuromodulation systems.	Data are acquired at a specific time-point, providing a snap-shot of brain structure or transient measure of function.



		Primary	Secondary Static	Secondary NBIA
Regular	Absolute number	26	31	21
	Percentage	21.1%	28.4%	67.7%
Irregular	Absolute number	89	73	10
	Percentage	72.4%	67%	32.3%
Bursting	Absolute number	8	5	0
	Percentage	6.5%	4.6%	0

		Primary	Secondary Static	Secondary NBIA
Regular	Absolute number	10	3	5
	Percentage	32.3%	7.7%	29.4%
Irregular	Absolute number	18	31	12
	Percentage	58.1%	79.5%	70.6%
Bursting	Absolute number	3	5	0
	Percentage	9.7%	12.8%	0

Chi square test P<0.001

Chi square test P=0.059

Figure 1 Black and White version

Legend to Figure 1

Heading: Pattern of Globus pallidus internus (GPi) and Globus pallidus externus (GPe) cell firing

Legend: Bar charts showing percentages of (A) GPi cells and (B) GPe cells for each dystonia group that were classified as regular irregular or bursting. Tables show absolute numbers and percentages of cells in each category. Chi-square tests showed a significant difference in the pattern of cell firing across the three main groups for the GPi cells but not for the GPe cells.

Source: McClelland VM, Valentin A, Rey HG, et al. Differences in globus pallidus neuronal firing rates and patterns relate to different disease biology in children with dystonia. J Neurol, Neurosurg, Psychiatry. 2016;87(9):958-67.